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(54) Title: CONTROLLED-RELEASE PHARMACEUTICALS PREPARED BY SUPERCRITICAL FLUID PROCESSING TECHNIQUES

(57) Abstract: Controlled-release pharmaceuticals are prepared by mixing starting materials and a process medium in a reactor to form a supercritical fluid slurry. The starting materials include a biologically active ingredient and a polymer. The process medium preferably is carbon dioxide which is supplied to the reactor in a supercritical state or which is heated and pressurized in the reactor to attain a supercritical state. After mixing for a period of time, the slurry either is left in the reactor or is discharged into a receiving vessel. The process medium is separated from the other materials and removed, leaving behind finely divided particles. The particles comprise porous particles of polymer that are infused with the biologically active ingredient. The finely divided particles can be incorporated into tablets, capsules, or the like for ingestion by patients.

CONTROLLED-RELEASE PHARMACEUTICALS PREPARED BY SUPERCRITICAL FLUID PROCESSING TECHNIQUES

BACKGROUND OF THE INVENTION

1. Field of the Invention.

The invention relates to the use of supercritical fluid processing techniques to prepare mixtures of pharmaceuticals with various polymeric excipients, particularly for the purpose of producing controlled-release pharmaceuticals.

2. Description of the Prior Art.

There is a continuing need for high quality pharmaceuticals, particularly pharmaceuticals whose active ingredient can be released gradually over an extended period of time or at a specific time during treatment. The phase "controlled-release" will be used herein to describe techniques to modify the rate at which active ingredients are released. Such techniques include delayed dissolution and diffusion control. Although controlled-release pharmaceuticals have been known for some time, they suffer from various drawbacks. One type of controlled-release pharmaceutical relies on micro encapsulation. In micro encapsulation, a very small particle or droplet of an active ingredient to be dispensed into a patient forms a core material that is coated with or embedded in an inert shell. The core material is released from the shell through erosion, permeation, or rupture of the shell. Variations in the thickness or material of the shell can be used to control the rate or timing with which the core material is released from the shell.

Micro encapsulation processes are very difficult and time-consuming to perform and often produce a large quantity of material that is out of specification. Although attempts have been made to improve micro encapsulation processes, certain difficulties remain. For example, in the process disclosed in U.S. 5,554,382, liposomes (micro capsules consisting of layers of lipids that encapsulate certain active substances such as enzymes) are produced by dissolving certain of the ingredients in solvents such as methanol, ethanol, and acetone. The use of solvents is undesirable due to the possibility of residual quantities of solvent being left in the micro capsule and thereafter released into the patient. In U.S. 5,766,637, a micro encapsulation process is disclosed that avoids the use of solvents, but the disclosed process still produces micro capsules which are believed to inherently suffer from a lack of consistency, and which therefore cannot release a drug into a patient at a uniform rate over a long period of time.

Another type of controlled-release pharmaceutical is a microscopic particle that is infused with an active ingredient. Such particles can be manufactured easier than micro capsules, and they have the potential to produce more uniform and predictable drug release. Numerous techniques are known to manufacture such particles, such techniques being exemplified by U.S. 5,424,076, U.S. 5,851,453, and U.S. 5,874,029, among others. Each of the referenced techniques relies on a solvent of some type to dissolve various ingredients, with the solvent being removed at a later stage of the process. As with the micro encapsulation technique referred to earlier, there is a possibility

that residual quantities of the solvent will remain in the particles and thereafter will be discharged into the patient. Even if the solvent is completely removed from the particles prior to completion of the manufacturing process, the use of such solvents causes the process to be more expensive and difficult to perform than desired.

Desirably, a process would be known that would produce microscopic particles that would release an active ingredient into a patient at a uniform rate over a long and predictable period of time. Any such process desirably would be easy to practice and would avoid the use of solvents completely.

SUMMARY OF THE INVENTION

In response to the foregoing concerns, the present invention provides an effective technique for the manufacture of controlled-release pharmaceuticals. Pharmaceutical mixtures according to the invention are prepared by charging a reactor with starting materials that include a biologically active ingredient and a polymer. A process medium is added to the reactor. The process medium preferably is carbon dioxide which is supplied to the reactor in a supercritical state or which is heated and pressurized in the reactor to attain a supercritical state. The heated and pressurized ingredients are mixed in the reactor for a period of time sufficient to form them into a homogeneous, gas-saturated suspension, or supercritical fluid slurry. After the ingredients have been mixed adequately, the slurry either is left in the reactor or is discharged into a receiving vessel where the process medium is separated from the remainder of the materials and removed, leaving finely divided particles behind.

The finely divided, engineered polymer particles are infused with the biologically active ingredient and can be incorporated into tablets, capsules, or the like for ingestion by patients. Typically, the pore sizes are designed to optimize the drug delivery profile. The sizes of the particles and the sizes of the pores can be controlled very accurately in order to dispense a known quantity of drugs or other biologically active ingredients at a uniform rate into a patient over a predictably long period of time. Due to the low temperature of the process, there will be little or no diminution of biologic activity of the biologically active ingredient.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a schematic view of apparatus suitable for practicing the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring now to FIG. 1, apparatus for practicing the present invention is indicated generally by the reference numeral 10. The apparatus 10 is described in U.S. Patent 5,399,597, entitled Method of Preparing Coating Materials, issued March 21, 1995 to Frederick S. Mandel, et al. Reference also is made to U.S. Patent 5,698,163, entitled Control System for Processes Using Supercritical Fluids, issued December 16, 1997 to Frederick S. Mandel, for a description of a control system for the apparatus 10. Additional details of the apparatus 10 can be found in U.S. Patent 6,054,103, entitled Mixing System for Processes Using Supercritical Fluids, issued to Frederick S. Mandel; U.S. application serial no. 09/315,616, entitled Delivery System for Processes Using Supercritical Fluids,

filed May 20, 1999 by Frederick S. Mandel; and U.S. Patent 5,993,747, entitled Mixing System for Processes Using Supercritical Fluids, issued November 30, 1999 to Frederick S. Mandel. The disclosures of all of the patents and applications referred to in this paragraph are incorporated in the present specification by reference.

Continuing to refer to FIG. 1, the apparatus 10 includes a reactor 12 that is connected by conduit 13 to a receiving vessel 14. A conduit 15 connects the reactor 12 to a source 16 of a process medium such as liquid carbon dioxide. The process medium preferably is fed under pressure into reactor 12 using a compressor or liquid pump 18. The receiving vessel 14 is connected by conduit 20 to a return tank 22. The return tank 22 is connected by conduit 24 to the source 16 of the process medium.

Reactor 12 includes, preferably at its base, a valve 26 for facilitating the emptying of the contents of the reactor 12 into the receiving vessel 14. A conduit 28 connects the top portion of the reactor 12 to conduit 20. A control valve 30 is included in conduit 28. A compressor 32 is included in conduit 20. Compressor 32 compresses and transfers gas emanating from the reactor 12 or the receiving vessel 14 into the return tank 22.

Reactor 12 includes a sealable opening or access port (not shown) that permits material to be charged into the reactor 12. Reactor 12 also includes a mechanical stirring device 34 for mechanically agitating and stirring the contents of reactor 12 so as to form a homogeneous mixture. Preferably, the access port is equipped with a quick-opening, breech-lock system that requires no hand tools

to open and close. Also, reactor 12 preferably includes a feed port having a valve (not shown) that facilitates the quick addition of minor amounts of material (e.g., polymer) to the reactor 12 once it has been pressurized.

Reactor 12 and receiving vessel 14 preferably are made of stainless steel. However, it will be appreciated that a number of alternative materials may be utilized, such as, for example, nickel-coated carbon steel or carbon steel vessels having chemically inert inserts or liners. A particularly desirable reactor 12 is shown in U.S. Patent 6,054,103, referred to previously.

The length of conduit 13 is minimized as much as possible. Conduit 13 can be in the form of a constant-diameter tubing. Alternatively, an orifice can be disposed in the conduit 13 just prior to receiving vessel 14. In another alternative, a header 36 can be disposed in conduit 13 just prior to receiving vessel 14. The header 36 includes a nozzle having multiple openings through which the homogeneous mixture is sprayed. Any number of nozzle openings may be employed to spray the slurry. Of course, it will be appreciated that the selection of the proper nozzle will be a function of various parameters, such as, for example, the pressure employed in reactor 12, the size of particles and flow rates desired, and the starting materials and process medium being used.

Typically, an orifice in the conduit 13 or the openings in a spray nozzle in the header 36 have a diameter of from about 0.001 inch to about 1 inch, preferably from about 0.005 inch to about 0.5 inch, and more preferably from about 0.01 inch to about 0.1 inch. Examples of suitable spray nozzles are hydraulic atomizing nozzles sold by Spraying Systems Co. of Wheaton, Ill.

Reference is made to application serial no. 09/315,616, referred to previously, for a disclosure of a particularly desirable control valve 26 and header 36.

Mechanical stirring device 34 comprises an electric motor 38 that drives a mixer 40. Mixer 40 may comprise any number of conventional mixing devices. The selection of the proper mixer will be a function of various parameters, such as, for example, the size of motor 38, the materials being mixed, the configuration of the reactor 12, the process medium being utilized and the pressure employed in vessel 12. An example of a suitable mixer 40 is a Cowles blade mixer sold by Indco, Inc. of New Albany, Indiana. Reference is made to U.S. Patent 6.054,103, referred to previously, for a disclosure of a particularly effective mixer 40. It will be appreciated that the present invention preferably provides for both distributive and dispersive mixing.

Apparatus 10 is employed in accordance with the present invention by first charging the starting materials for the pharmaceutical that one desires to produce into the reactor 12. Reactor 12 then is sealed and isolated. The process medium from source 16 then is fed into reactor 12 via conduit 15 until a suitable quantity has been introduced into reactor 12. A critical temperature can be attained by heating reactor 12, heating the liquid/gas stream as it enters reactor 12, by agitating reactor 12, or by combinations of these techniques. The pressure and temperature in reactor 12 converts the process medium into a supercritical fluid.

Reactor 12 is maintained at an internal temperature of about -85°C. to about 200°C. When utilizing CO_2 as a process medium, a temperature of about

15°C. to about 160°C. is employed, and preferably about 20°C. to about 150°C., and more preferably about 31°C. to about 100°C. The particular temperature utilized will be a function of various variables such as, for example, the gas utilized, the composition of the starting materials, the pressures employed and equipment configurations. Pressure from about 350 psi to about 20,000 psi may be utilized. When employing a gas such as CO_2, a pressure of about 550 psi to about 7000 psi is utilized, and preferably about 950 psi to about 5000 psi, and more preferably about 1080 psi to about 4500 psi. The particular pressure utilized will be a function of such variables as the temperature of the reactor 12 and the particular process medium utilized.

Once reactor 12 has been heated and pressurized, motor 38 is energized and the starting materials and the supercritical fluid are thoroughly mixed to form a homogeneous, gas-saturated suspension, otherwise referred to as a supercritical fluid slurry. Preferably, reactor 12 is held below the melting point of the materials being processed. The temperature in reactor 12 preferably is in the range of from about 5 degrees below the T_g (i.e., glass transition temperature) of at least one of the materials being processed up to about the melting point of such one material. In the case of an amorphous material, "melting point" means the temperature at which the material become wholly fluid. It is believed that a supercritical fluid will suppress the T_g of most materials. In order to attain the desired temperature in reactor 12, reactor 12 may be equipped with a heat exchanger or other suitable heating/cooling means.

The starting materials are mixed in reactor 12 for a period of about 1 to about 480 minutes, preferably about 5 to about 300 minutes and more preferably from about 30 to about 240 minutes. The viscosity of the supercritical fluid slurry is a function of the temperature and the density of the process medium. Once the starting materials have been thoroughly mixed, valve 26 is opened rapidly to minimize the pressure drop at valve 26. The pressurized supercritical fluid pushes the slurry out of the reactor 12. Valve 26 is maintained in the open position until such time as receiving vessel 14 (which is maintained at a lower pressure than reactor 12) has been filled and reactor 12 has been emptied of its contents. It has been found that best results are obtained if the flow within conduit 13 upstream of the header 36 is entirely turbulent with a pressure drop across the conduit of 18 psi or less. Once receiving vessel 14 has been filled and substantially all of the starting materials have been transferred, valve 30 is opened in order to depressurize reactor 12 and permit the flow of gaseous process medium into return tank 22. The recycled process medium is made available for purposes of reuse by being transferred via conduit 24 to conduit 15.

While the slurry is being transferred to receiving vessel 14, receiving vessel 14 is held at a constant pressure. Preferably the pressure in receiving vessel 14 is lower than that in the reactor 12 so that the slurry enters receiving vessel 14 at a very high rate. Receiving vessel 14 is maintained at a starting temperature of about -85°C. to about 220°C., preferably about -18°C. to about 160°C., and more preferably about 0°C. to about 130°C. As with reactor 12, in order to maintain the desired temperature in receiving vessel 14, a heat

exchanger or other cooling/heating device may be necessary. Preferably, receiving vessel 14 is maintained at a temperature below the melting point of the materials being processed. Receiving vessel 14 is maintained at a pressure of about 0 psi to about 5000 psi, preferably about 100 psi to about 2000 psi, and more preferably about 150 psi to about 1000 psi. The particular pressure and temperature utilized in receiving vessel 14 are a function of various variables, such as the particular process medium utilized and the composition of the starting materials.

The present invention uses a process medium that is capable of achieving a supercritical state. As used herein, the phrase "supercritical fluid" means a material that at specific temperatures and pressures no longer displays the properties of either a gas or a liquid. Examples of potential supercritical fluids suitable for use with the present invention include carbon dioxide and nitrous oxide. The critical properties for these compounds are set forth below. The present invention contemplates the use of these compounds either by themselves or in combination.

Compound	Critical Temperature (°C.)	Critical Pressure (psi)
CO_2	31.3	1071.34
N_2O	36.5	1053.70
CHF_3	26.2	714.42
$CHClF_2$	96.2	730.59
CH_3OCH_3	126.9	770.28
CH_3OH	239.5	1190.70
C_2H_5OH	243.1	937.86
Xe	16.6	858.48
H_2O	374.2	3241.35
NH_3	132.5	1658.16

One compound that is particularly well suited for use with the present invention is carbon dioxide (CO_2). Carbon dioxide is preferred because it is non-toxic, nonflammable, reasonably priced, and is easily separated or removed from the constituents used in making pharmaceuticals at the contemplated temperatures and pressures. Therefore, there will be no residual CO_2 in the finished products that could contribute to problems when used as pharmaceuticals. Also, the critical temperature of CO_2 is sufficiently low that the biologically active materials used in the process will not be affected adversely.

Although various process media may be used to produce pharmaceutical mixtures in accordance with the principles of the present invention, care must be taken not to utilize starting materials that are soluble in the process medium at operating temperatures and pressures. If the starting materials are soluble in the process medium, it will not be possible to transfer the starting materials to the

receiving vessel 14 without losing some of the starting materials to the storage tank 22, which would be a very undesirable result.

Starting materials that are used in the present invention are polymers that have a low melting temperature and which are capable of being formed into microscopic particles having suitable porosity to accept a biologically active material. Because the pharmaceuticals produced by the present invention are intended for use in the human body, potentially harmful additives such as pigments, flow control agents, extenders, and the like should not be used. Categories of acceptable polymers include thermoplastic, thermoset, or a combination of both. Polymers suitable for use in controlled drug release are discussed in K. Ulrich, et al., Polymeric Systems for Controlled Drug Release, Journal of the American Chemical Society (1999)("the Polymer Article"). It is believed that such polymers are suitable for use with the present invention. As noted in the Polymer Article, categories of suitable polymers include polyesters, polyorthoesters, polyanhydrides, polyamides, and phosphorous-containing polymers. It has been found that hydroxy-methyl cellulose and derivative-type polymers (e.g., hydroxy propyl cellulose) and polylactide-co-glycolide (e.g., Medisorb 8515 DL High I.V.) function well as part of the present invention. Other suitable polymers as specified in the Polymer Article include polyethylene, polypropylene, polyvinyl chloride, polyvinyl alcohol, polyethylene-vinyl acetate, polyenol-ketone, polyacrylic acid, polycarbophil, polyacrylamides, poly-N-isopropyl acrylamide, polyacrylates, polyethylene glycol, polyglycolic acid, polylactic acid, poly-ϵ-caprolactone, poly-3-hydroxybutyrate, polyortho esters,

polyanhydrides, polyamino acids, pseudo-polyamino acids, polyamide-enamines, polyamido amines, polyurethanes, azopolymers, polydimethylsiloxane, and polyphosphazenes.

Biologically active ingredients suitable for use with the present invention include inorganic or organic molecules, peptides, proteins, oligosaccharides, carbohydrates, nucleic acids, steroidals, and small molecules such as aspirin, morphine, steroids, anti-diarrheals, anti-diabetics, etc. The biologically active ingredients can include compounds that treat the following:

1. Infections: antiviral drugs, antibacterial drugs, antifungal drugs, and anthelmintics.
2. Cardiovascular system: positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, calcium channel blockers, sympathomimetics, anticoagulants, anti-platelet drugs, fibrinolytic drugs, and lipid-lowering drugs.
3. Gastro-intestinal system: antacids, antispasmodics, ulcer-healing drugs, anti-diarrheals drugs, and laxatives.
4. Central nervous system: hypnotics and anxiolytics, anti-psychotics, antidepressants, central nervous system stimulants, appetite suppressants, drugs used to treat nausea and vomiting, analgesics, anti-epileptics, drugs used in parkinsonism, and drugs used in substance dependence.

5. Malignant disease and immunosuppresion: cytotoxic drugs, immune response modulators, and sex hormones and antagonists of malignant diseases.

6. Respiratory system: bronchodilators, corticosteroids, cromoglycate and related therapy, antihistamines, respiratory stimulants, pulmonary surfactants, and systemic nasal decongestants.

7. Musculoskeletal and joint diseases: drugs used in rheumatic diseases, and drugs used in neuromuscular disorders.

8. Immunological products and vaccines.

Pharmaceutical mixtures produced in accordance with the present invention can be fabricated into tablets, powders, granules, capsules, suppositories, pessaries, colloidal suspensions, matrices, gels, micro-particles, monoliths, pastes, and creams. The pharmaceuticals can be administered by pulmonary, oral, rectal, parenteral, epicutaneous, or mucosal routes. Delivery of active ingredients may be accomplished via a series of methods including modified release via polymer biosorption or enhanced release via extended surface area. Active drugs can be placed in biosorption matrices at concentrations from 0.5% to 99%. The levels can be modified from below percolation threshold to well above. For the high threshold materials, many of the biosorbable polymers have from 25 to 100% pore interconnectivity which provides an additional mechanism for drug release.

When CO_2 gas is utilized as a process medium, CO_2 is charged to or utilized in reactor 12 so as to provide from about 1.0% by weight to about 99.0%

by weight CO_2 and from about 99.0% by weight to about 1.0% by weight starting materials, preferably from about 20% by weight to about 80% by weight CO_2 and from about 80% by weight to about 20% by weight starting materials, and more preferably from about 40% by weight to about 60% by weight CO_2 and from about 60% by weight to about 40% by weight starting materials. After processing, the materials in receiving vessel 14 are a collection of homogeneous, uniformly sized, engineered polymer particles. In the unlikely event that any oversize particles or an agglomeration of particles (foam) are contained in receiving vessel 14, the product must be rejected.

The amount of carbon dioxide absorbed and hence the amount of polymer swelling is proportional to temperature and pressure. For an amorphous polymer system the swelling could be as much as 66% or greater. This swelling leaves a large void volume within the polymer. As the polymer is reduced to ambient conditions, the rate of degassing or depressurization can influence the pore size of the particles as well as the size of the particles themselves. The depressurization is accomplished by way of controlled release from the receiving vessel 14 and a variable rate can be set. The density of the swollen polymer usually is equalized to that of the supercritical fluid density of the process medium. This permits the starting materials to be suspended in a mixture of equivalent density. If atomization is carried out, a range of materials can be produced that possess high surface areas with relatively low surface areas as well. The high surface area materials will give an immediate dosage of the biologically active material whereas the low surface area materials will require

significant biosorption before release of the biologically active material to the host system. Rapid or slow degassing of the mixture can further induce additional control of the formulation's release characteristics.

Although the apparatus 10 has been described as including various components downstream of the reactor 12 such as the conduit 13, receiving vessel 14, flush valve 26, etc., it is possible to produce acceptable product according to the invention without any such components. Suitable product can be prepared merely by mixing the supercritical fluid slurry in the reactor 12 and then releasing the internal pressure in a controlled manner. However, use of the components downstream of the reactor 12, particularly orifices or nozzles in the conduit 13, enables accurate control of particle size to be attained more easily. Because the particle size can be controlled accurately, pharmaceuticals having predictable, desired characteristics can be produced easily.

The following Examples describe a method of producing pharmaceuticals within the scope of the present invention. Except as noted, the apparatus used in the following Examples employed the reactor 12, but did not include downstream components such as the flush valve 26, conduit 13, or receiving vessel 14. Unless otherwise indicated, all parts and percentages are by weight and all temperatures are in degrees Centigrade (°C.).

EXAMPLE 1

Seven (7) grams of an enzyme, catalase, and seven (7) grams of PLGA polymer (RG755) were premixed and charged into a 250 ml TEFLON beaker. The beaker was placed in reactor 12. Reactor 12 was filled with 6.2 pounds of

liquid CO_2 from source 16. The source 16 of CO_2 is a standard commercial source maintained at a temperature of about -18°C. and a pressure of about 300 psi. The reactor 12 was heated to 38°C at a pressure of 1700 psi, thereby rendering the CO_2 a supercritical fluid. The starting materials and supercritical fluid were maintained under these conditions while being mixed for 20 minutes using agitation device 34. The mixer 40 was rotated at a rate of 78 rpm.

Upon completion of mixing as described, the CO_2 was released from reactor 12 until ambient pressure was attained. During pressure release, the reactor 12 was cooled with water. The reactor 12 was opened to yield a cake composed of finely divided particles, each containing 50% enzyme and 50% polymer.

The experiment was repeated with an enzyme of different particle size. The experiment also was repeated with a different polymer (RG752). A control experiment also was performed to test the effect of the process on the enzyme only, without a polymer. Standard enzyme activity tests showed a minimal reduction in enzyme activity due to performance of the process.

Suitable material ranges for the enzyme starting material are 1-99% and 1-99% for the polymer starting material (PCL or PLGA). The pressure in the reactor 12 can be varied between 290-14,500 psi, the temperature can vary between 0-127°C, and the mixing rate can vary between 1-150 rpm.

EXAMPLE 2

A series of experiments were conducted to vary the ratio of enzyme to polymer. Catalase to PLGA (RG755) ratios from 5:95 to 40:60 were tested. In each experiment, the mixture was charged into a 250 ml TEFLON beaker that was placed into a one-gallon reactor 12. Reactor 12 was filled with liquid CO_2 from source 16. The filled reactor 12 was heated to 38°C and pressurized to pressures within the range of 1800-2200 psi, thereby rendering the CO_2 a supercritical fluid. The starting materials and supercritical fluid were maintained under these conditions while being mixed for 30 minutes using agitation device 34. The mixer 40 was rotated at a rate of about 80 rpm. Upon completion of mixing as described, water was turned on to cool the system as CO_2 was released from the reactor 12 until ambient pressure was attained. The reactor 12 was opened to yield a monolithic, porous product.

Another experiment was conducted under similar process conditions in which a mixture having a catalase-to-PLGA ratio of 30:70 was heated to 39°C at 2350 psi. The mixer 40 was rotated at 80 rpm for 30 minutes. As in the other experiments, the reactor 12 was cooled while the CO_2 was released to yield a monolithic, porous product.

Suitable material ranges for the catalase enzyme starting material are 1-99% and 1-99% for the PCL/PLGA polymer starting material. The pressure in the reactor 12 can be varied between 290-14,500 psi, the temperature can vary between 0-127°C, and the mixing rate can vary between 1-150 rpm.

EXAMPLE 3

Approximately 35 experiments were performed to disperse a CO_2-insoluble dye as a model for a drug into a biodegradable polymer. In one experiment, 92% PCL and 8% sodium fluorescein (dye content about 70%) were used to prepare a batch weighing 207 grams. The mixture was charged into a one-gallon reactor 12 to which a receiving vessel 14 was connected by a conduit 13. Reactor 12 was sealed, filled with 6.3 pounds of liquid CO_2 from source 16, and heated to 50°C at a pressure of 2770 psi, thereby rendering the CO_2 a supercritical fluid. The starting materials and supercritical fluid were maintained under these conditions while being mixed for 75 minutes using agitation device 34. The mixer 40 was rotated at a rate of 150 rpm. Thereafter, the flush valve 26 was opened and the mixture was transferred through the conduit 13 (heated to 50°C). The mixture was atomized into the vessel 14. Controlled release studies were conducted on the recovered product.

In another experiment, 3.3 grams of sodium fluorescein and 6.7 grams of PLGA (Medisorb 8515 DL High I.V.) Were loaded into the volume-reducing conical insert of reactor 12. Reactor 12 was sealed, filled with 6.4 pounds of liquid CO_2 from source 16, and heated to 40°C at a pressure of 3400 psi, thereby rendering the CO_2 a supercritical fluid. The starting materials and supercritical fluid were maintained under these conditions while being mixed for one hour using agitation device 34. The mixer 40 was rotated at a rate of 55 rpm. Thereafter, the flush valve 26 was opened and the mixture was transferred through the conduit 13 (heated to 50°C). The mixture was atomized into the

vessel 14 to produce 4.5 grams of finely divided powder. Controlled release studies were conducted on the recovered product.

Suitable material ranges for the sodium fluorescein starting material are 1-99% and 1-99% for the PCL/PLGA polymer starting material. The pressure in the reactor 12 can be varied between 290-14,500 psi, the temperature can vary between 0-127°C, and the mixing rate can vary between 1-150 rpm.

EXAMPLE 4

An anti-cancer drug (Gooserlein Acetate) and a biodegradable PLGA (Medisorb 9505 L) were mixed to produce a batch weighing 10 grams. The mixture was loaded into the volume-reducing conical insert of reactor 12. Reactor 12 was sealed, filled with 6.4 pounds of liquid CO_2 from source 16, and heated to 40°C at a pressure of 3100 psi, thereby rendering the CO_2 a supercritical fluid. The starting materials and supercritical fluid were maintained under these conditions while being mixed for one hour using agitation device 34. The mixer 40 was rotated at a rate of 108 rpm. Thereafter, the flush valve 26 was opened and the mixture was transferred through the conduit 13 (heated to 50°C). The mixture was atomized into the vessel 14 to produce a finely divided powder.

Suitable material ranges for the anti-cancer starting material are 1-36% and 64-99% for the PLGA polymer starting material. The pressure in the reactor 12 can be varied between 290-14,500 psi, the temperature can vary between 0-127°C, and the mixing rate can vary between 1-150 rpm.

Although the invention has been described in its preferred form with a certain degree of particularity, it will be understood that the present disclosure of the preferred embodiment has been made only by way of example, and that various changes may be resorted to without departing from the true spirit and scope of the invention as hereinafter claimed. It is intended that the patent shall cover, by suitable expression in the appended claims, whatever features of patentable novelty exist in the invention disclosed.

What is claimed is:

1. A method for manufacturing controlled-release pharmaceuticals, comprising:

providing a reactor having a mixer;

charging the reactor with starting materials that include a biologically active ingredient and a polymer;

providing supercritical fluid in the reactor;

mixing the starting materials and the supercritical fluid in the reactor for a period of time sufficient to form a supercritical fluid slurry;

reducing the pressure in the reactor to ambient; and

recovering controlled-release pharmaceuticals from the reactor.

2. The method of claim 1, wherein the supercritical fluid is selected from the group consisting of carbon dioxide and nitrous oxide.

3. The method of claim 1, wherein the step of providing supercritical fluid in the reactor is accomplished by charging a liquid into the reactor, and thereafter heating and pressurizing the reactor contents so that the liquid attains a supercritical state.

4. The method of claim 3, wherein the liquid is carbon dioxide.

5. The method of claim 4, wherein the carbon dioxide is heated to a temperature within the range of 0-127°C and is pressurized to a pressure within the range of 290-14,500 psi.

6. The method of claim 1, wherein, during the step of mixing, the reactor is maintained at a temperature below the melting point of the starting materials.

7. The method of claim 1, wherein the biologically active ingredient is selected from the group consisting of antiviral drugs, antibacterial drugs, antifungal drugs, anthelmintics, positive intropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, calcium channel blockers, sympathomimetics, anticoagulants, anti-platelet drugs, fibrinolytic drugs, lipid-lowering drugs, antacids, antispasmodics, ulcer-healing drugs, anti-diarrheals drugs, laxatives, hypnotics and anxiolytics, anti-psychotics, antidepressants, central nervous system stimulants, appetite suppressants, drugs used to treat nausea and vomiting, analgesics, anti-epileptics, drugs used in parkinsonism, drugs used in substance dependence, cytotoxic drugs, immune response modulators, and sex hormones and antagonists of malignant diseases, bronchodilators, corticosteroids, cromoglycate and related therapy, antihistamines, respiratory stimulants, pulmonary surfactants, and systemic nasal decongestants, drugs used in rheumatic diseases, and drugs used in neuromuscular disorders, immunological products and vaccines.

8. The method of claim 1, wherein the polymer is a thermoplastic polymer, a thermoset polymer, or a combination of thermoplastic and thermoset polymers.

9. The method of claim 8, wherein the polymer is selected from the group consisting of hydroxy-methyl cellulose and its derivatives, polylactide-co-glycolide, polyethylene, polypropylene, polyvinyl chloride, polyvinyl alcohol, polyethylene-vinyl acetate, polyenol-ketone, polyacrylic acid, polycarbophil, polyacrylamides, poly-N-isopropyl acrylamide, polyacrylates, polyethylene glycol, polyglycolic acid, polylactic acid, poly-ϵ-caprolactone, poly-3-hydroxybutyrate, polyortho esters, polyanhydrides, polyamino acids, pseudo-polyamino acids, polyamide-enamines, polyamido amines, polyurethanes, azopolymers, polydimethylsiloxane, and polyphosphazenes.

10. The method of claim 1, wherein the step of mixing is accomplished by a blade or helical mixer.

11. The method of claim 10, wherein the mixer is rotated at a speed within the range of 1-150 rpm.

12. A method for manufacturing controlled-release pharmaceuticals, comprising:

providing a reactor having a mixer;

providing a receiving vessel and a conduit that connects the reactor and the receiving vessel;

charging the reactor with starting materials that include a biologically active ingredient and a polymer;

providing supercritical fluid in the reactor;

mixing the starting materials and the supercritical fluid in the reactor for a period of time sufficient to form a supercritical fluid slurry;

discharging the slurry into the receiving vessel through the conduit;

reducing the pressure in the receiving vessel to ambient; and

recovering controlled-release pharmaceuticals from the receiving vessel.

13. The method of claim 12, wherein the supercritical fluid is selected from the group consisting of carbon dioxide and nitrous oxide.

14. The method of claim 12, wherein the step of providing supercritical fluid in the reactor is accomplished by charging a liquid into the reactor, and thereafter heating and pressurizing the reactor contents so that the liquid attains a supercritical state.

15. The method of claim 14, wherein the liquid is carbon dioxide.

16. The method of claim 15, wherein the carbon dioxide is heated to a temperature within the range of 0-127°C and is pressurized to a pressure within the range of 290-14,500 psi.

17. The method of claim 12, wherein, during the step of mixing, the reactor is maintained at a temperature below the melting point of the starting materials.

18. The method of claim 12, wherein the biologically active ingredient is selected from the group consisting of antiviral drugs, antibacterial drugs, antifungal drugs, anthelmintics, positive intropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, calcium channel blockers, sympathomimetics, anticoagulants, anti-platelet drugs, fibrinolytic drugs, lipid-lowering drugs, antacids, antispasmodics, ulcer-healing drugs, anti-diarrheals drugs, laxatives, hypnotics and anxiolytics, anti-psychotics, antidepressants, central nervous system stimulants, appetite suppressants, drugs used to treat nausea and vomiting, analgesics, anti-epileptics, drugs used in parkinsonism, drugs used in substance dependence, cytotoxic drugs, immune response modulators, and sex hormones and antagonists of malignant diseases, bronchodilators, corticosteroids, cromoglycate and related therapy, antihistamines, respiratory stimulants, pulmonary surfactants, and systemic nasal decongestants, drugs used in rheumatic diseases, and drugs used in neuromuscular disorders, immunological products and vaccines.

19. The method of claim 12 wherein the polymer is a thermoplastic polymer, a thermoset polymer, or a combination of thermoplastic and thermoset polymers.

20. The method of claim 19, wherein the polymer is selected from the group consisting of hydroxy-methyl cellulose and its derivatives, polylactide-co-glycolide, polyethylene, polypropylene, polyvinyl chloride, polyvinyl alcohol, polyethylene-vinyl acetate, polyenol-ketone, polyacrylic acid, polycarbophil, polyacrylamides, poly-N-isopropyl acrylamide, polyacrylates, polyethylene glycol, polyglycolic acid, polylactic acid, poly-ϵ-caprolactone, poly-3-hydroxybutyrate, polyortho esters, polyanhydrides, polyamino acids, pseudo-polyamino acids, polyamide-enamines, polyamido amines, polyurethanes, azopolymers, polydimethylsiloxane, and polyphosphazenes.

21. The method of claim 12, further comprising the step of providing an orifice in the conduit.

22. The method of claim 21, wherein the orifice has a diameter within the range of about 0.01 inch to about 0.10 inch.

23. The method of claim 12, further comprising the step of providing a nozzle having multiple openings in the conduit.

24. The method of claim 23, wherein the openings in the nozzle have a diameter within the range of about 0.01 inch to about 0.10 inch.

25. The method of claim 12, wherein the step of mixing is accomplished by a blade or helical mixer.

26. The method of claim 25, wherein the mixer is rotated at a speed within the range of 1-150 rpm.

27. A controlled-release pharmaceutical produced by the method of claim 1.

28. A controlled-release pharmaceutical produced by the method of claim 12.

29. A pharmaceutical mixture, comprising:

engineered polymer particles containing a biologically active ingredient, the particles capable of being biosorbed over a predetermined period of time.

30. The pharmaceutical mixture of claim 29, wherein the particles contain pores and the biologically active ingredient is dispersed within the pores.

31. The pharmaceutical mixture of claim 29, wherein the biologically active ingredient is selected from the group consisting of antiviral drugs, antibacterial drugs, antifungal drugs, anthelmintics, positive intropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, calcium channel blockers, sympathomimetics, anticoagulants, anti-platelet drugs, fibrinolytic drugs, lipid-lowering drugs, antacids, antispasmodics, ulcer-healing drugs, anti-diarrheals drugs, laxatives, hypnotics and anxiolytics, anti-psychotics, antidepressants, central nervous system stimulants, appetite suppressants, drugs used to treat nausea and vomiting, analgesics, anti-epileptics, drugs used in parkinsonism, drugs used in substance dependence, cytotoxic drugs, immune response modulators, and sex hormones and antagonists of malignant diseases, bronchodilators, corticosteroids, cromoglycate and related therapy, antihistamines, respiratory stimulants, pulmonary surfactants, and systemic nasal decongestants, drugs used in rheumatic diseases, and drugs used in neuromuscular disorders, immunological products and vaccines.

32. The pharmaceutical mixture of claim 29, wherein the polymer is a thermoplastic polymer, a thermoset polymer, or a combination of thermoplastic and thermoset polymers.

33. The pharmaceutical mixture of claim 32, wherein the polymer is selected from the group consisting of hydroxy-methyl cellulose and its derivatives, polylactide-co-glycolide, polyethylene, polypropylene, polyvinyl

chloride, polyvinyl alcohol, polyethylene-vinyl acetate, polyenol-ketone, polyacrylic acid, polycarbophil, polyacrylamides, poly-N-isopropyl acrylamide, polyacrylates, polyethylene glycol, polyglycolic acid, polylactic acid, poly-ϵ-caprolactone, poly-3-hydroxybutyrate, polyortho esters, polyanhydrides, polyamino acids, pseudo-polyamino acids, polyamide-enamines, polyamido amines, polyurethanes, azopolymers, polydimethylsiloxane, and polyphosphazenes.

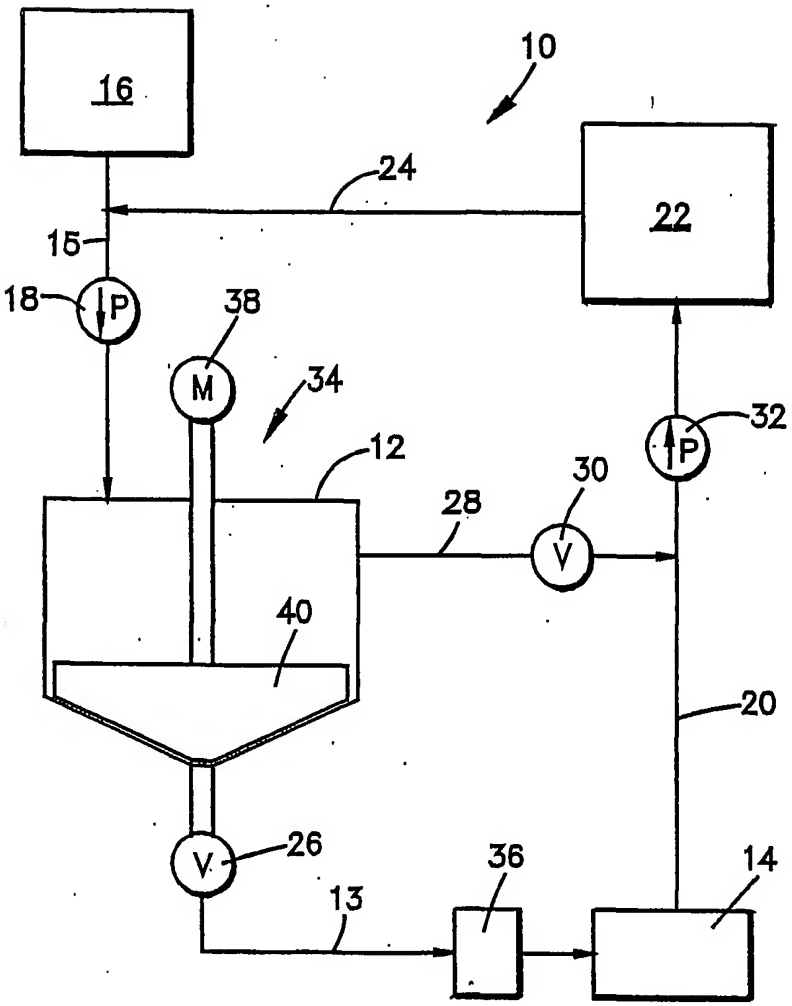

Fig.1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/26383

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C08F 6/00; A61M 9/00; B65D 37/00
US CL : 128/200.23; 222/207; 523/307, 340; 528/501

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 128/200.23; 222/207; 523/307, 340; 528/501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,399,597 A (MANDEL et al) 21 March 1995 (21.03.1995), see entire document.	1-6,8-10,12-17,19-25,27-33 --- 1-6,8-17,19-33
Y	US 5,301,664 A (SIEVERS et al) 12 April 1994 (12.04.1994), see entire document.	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 October 2001 (05.10.2001)	17 JAN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Amy E. Pulliam Telephone No. (703) 308-1234

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